Identification of Oct4-activating compounds that enhance reprogramming efficiency.

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Public Summary:
One of the hurdles for clinical application of induced pluripotent stem cells (iPSC) is the low efficiency and slow process of reprogramming, a process of converting somatic cells, such as skin fibroblasts, into embryonic stem cell-like state. In this study, we identified a novel small molecule compound, termed Oct4-activating compound 1 (OAC1), that activates the promoters of both Oct4 and Nanog, two molecules that play important role in maintaining embryonic stem cell-like state. Furthermore, when added to the reprogramming mixture along with the quartet reprogramming factors (Oct4, Sox2, c-Myc, and Klf4), OAC1 enhanced the efficiency and accelerated the process of converting fibroblast cells into embryonic stem cell-like state. The iPSC colonies derived using the Oct4-activating compounds along with the quartet factors exhibited typical embryonic stem cell morphology, gene-expression pattern, and developmental potential. OAC1 seems to enhance reprogramming efficiency in a unique manner, independent of the known signaling pathways that facilitate the reprogramming process.

Scientific Abstract:
One of the hurdles for practical application of induced pluripotent stem cells (iPSC) is the low efficiency and slow process of reprogramming. Octamer-binding transcription factor 4 (Oct4) has been shown to be an essential regulator of embryonic stem cell (ESC) pluripotency and key to the reprogramming process. To identify small molecules that enhance reprogramming efficiency, we performed a cell-based high-throughput screening of chemical libraries. One of the compounds, termed Oct4-activating compound 1 (OAC1), was found to activate both Oct4 and Nanog promoter-driven luciferase reporter genes. Furthermore, when added to the reprogramming mixture along with the quartet reprogramming factors (Oct4, Sox2, c-Myc, and Klf4), OAC1 enhanced the iPSC reprogramming efficiency and accelerated the reprogramming process. Two structural analogs of OAC1 also activated Oct4 and Nanog promoters and enhanced iPSC formation. The iPSC colonies derived using the Oct4-activating compounds along with the quartet factors exhibited typical ESC morphology, gene-expression pattern, and developmental potential. OAC1 seems to enhance reprogramming efficiency in a unique manner, independent of either inhibition of the p53-p21 pathway or activation of the Wnt-beta-catenin signaling. OAC1 increases transcription of the Oct4-Nanog-Sox2 triad and Tet1, a gene known to be involved in DNA demethylation.

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